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FIFTEEN-MINUTE CONSULTATION: WHEN TO SUSPECT LIVER DISEASE

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ABSTRACT

Liver disease have protean presentations: acute liver failure, insidious chronic liver disease, or an incidental finding of abnormal liver function tests. In this article we discuss the identification of liver disease and 'red flags' in four specific clinical situations: conjugated prolonged jaundice; acute liver failure; new-onset jaundice in a teenager; and incidental finding of abnormal aminotransferases. These scenarios are used to illustrate how ancillary investigations aid diagnosis.

INTRODUCTION

Liver disease in children has varied presentation, ranging from the frequently encountered prolonged, neonatal jaundice to the comparatively rare acute liver failure. Due to the supra-regional specialisation of UK hepatology services, many paediatricians may not have extensive clinical exposure to these conditions. This article will focus on how blood tests may be interpreted in clinical context to identify important liver pathologies.

Liver function tests (LFTs) are among the most frequently performed blood tests in children. They are often requested as part of an automated biochemistry panel, which results in incidental identification of abnormalities. Whilst they may be valuable first-line investigations in the assessment of liver disease, they usually do not test the functional capacity of the liver, nor are abnormalities necessarily specific for individual liver diseases, though some patterns may be observed.

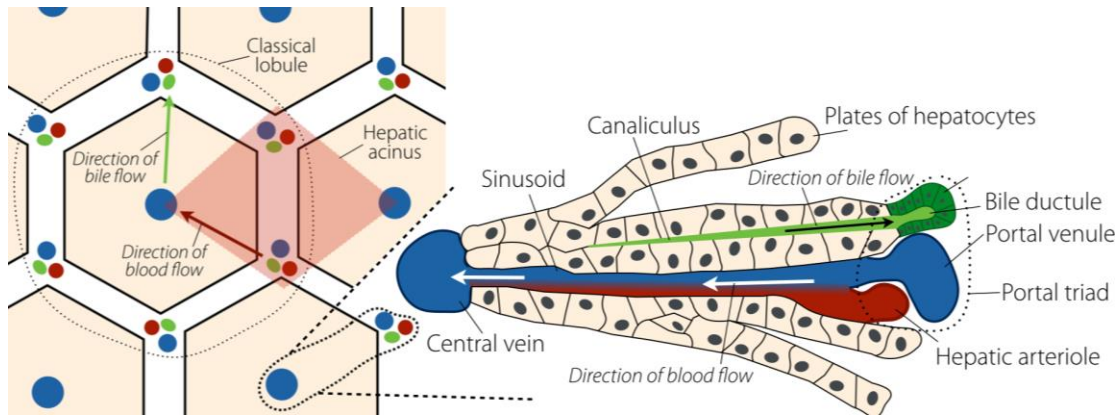
Due to the liver's considerable functional reserve, liver disease often remains subclinical until relatively advanced[1,2]. Therefore, in addition to patients with symptoms or signs of liver disease (e.g. jaundice, splenomegaly), evidence of liver (dys)function should be actively sought in certain groups of patients, including: hepatotoxic medication (e.g. methotrexate) and systemic conditions that may affect the liver (e.g. ulcerative colitis with associated sclerosing cholangitis, or obesity and NAFLD).

BACKGROUND PATHOPHYSIOLOGY

Appropriate requesting and interpretation of liver function tests requires an understanding of hepatobiliary cellular structure, liver physiology, and non-liver sources of certain enzymes or proteins measured by LFTs.

Liver microanatomy and physiology

The functional unit of the liver is the hepatocyte. Plates of hepatocytes comprise the hepatic lobule, with portal tracts at the periphery and a central vein in the middle (see figure 1). Arterial and portal venous blood mixes in sinusoids that run either side of plates of hepatocytes. Hepatocytes secrete products for excretion into bile in canaliculi (formed from the lateral wall of hepatocytes), which drains into bile ducts. Cholangiocytes (biliary epithelial cells) line bile ducts and the remainder of the biliary system.

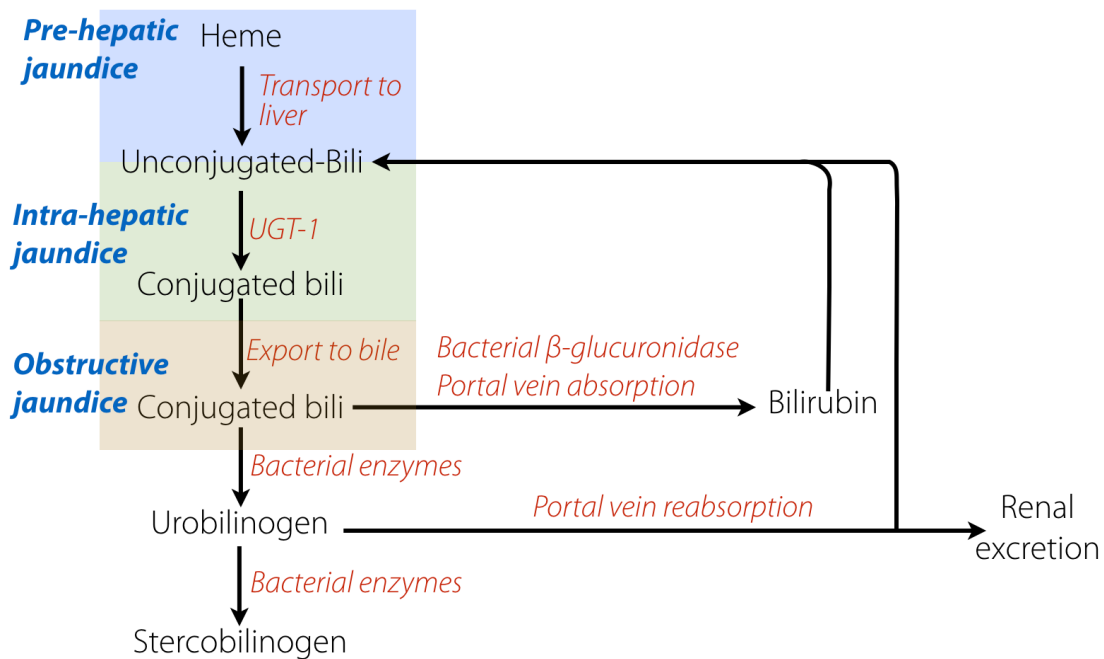


<Figure 1>

There are several key functions of the liver, including synthetic, metabolic, production of bile, and detoxification. Though variable, end-stage chronic liver disease tends to manifest in blood tests as coagulopathy and hypoalbuminaemia, whilst acute liver failure results in coagulopathy, hypoglycaemia, and hyperbilirubinaemia. The degree of abnormality of INR, albumin, pH, lactate, bilirubin, and glucose does correlate with the degree of hepatic dysfunction.

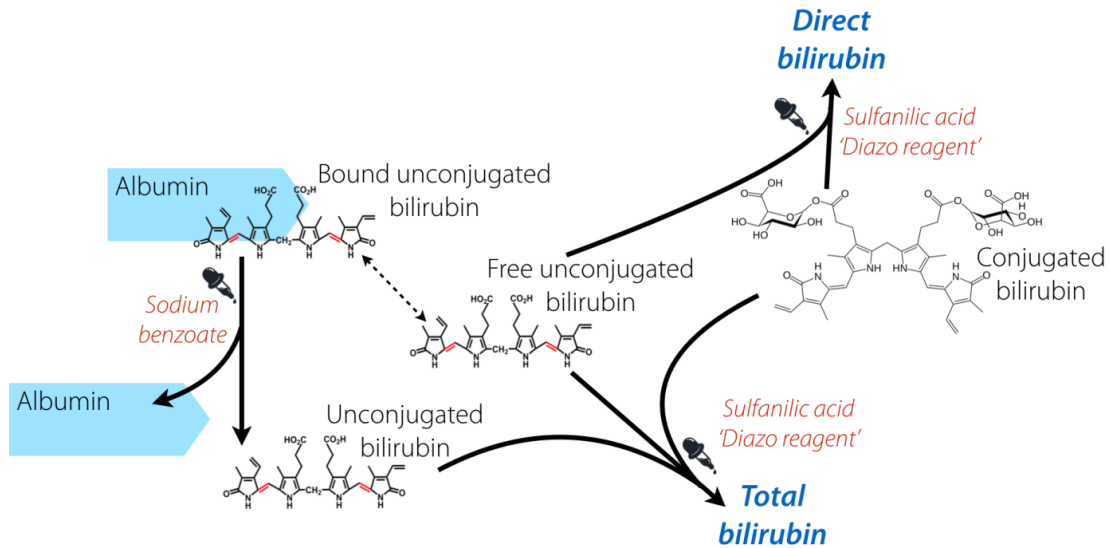
Bilirubin

Bilirubin is the breakdown product of haem, 95% of which comes from red cell haemoglobin. It is produced as unconjugated bilirubin by the reticuloendothelial system and transported to hepatocytes, where it is converted to conjugated bilirubin before being exported into canaliculi (see figure 2.).



<Figure 2>

Serum bilirubin may be measured in total, or split into conjugated and total forms. Measurement of direct bilirubin is assumed to be synonymous with conjugated bilirubin, however there is a small amount of unconjugated bilirubin unbound to albumin ('free'), which will also react (see figure 3). The greater the total bilirubin, the more free unconjugated bilirubin will be present. Therefore, the higher the total bilirubin, the more the direct bilirubin will be influenced by unconjugated bilirubin[3].



<Figure 3>

Liver enzymes

The enzymes that comprise the typical biochemical panel of LFT are not only expressed in the liver (see table 1). Hence, AST/ALT elevation could be of muscle origin and concomitant CK measurement is usually helpful to attribute the aminotransferase rise to muscle disease[3]. Mild elevations of ALT and AST occur in almost any liver condition, however, the degree of increase in aminotransferases does not give useful information about liver function or underlying diagnosis.

Enzyme	Source
Aminotransferases	AST - Liver, heart, skeletal muscle, kidney, pancreas, red cells ALT – Liver, skeletal muscle, heart
ALP	Bone, small intestine, liver, placenta, kidney
GGT	Biliary epithelial, hepatocytes, renal tubules, pancreas, brain, breast, small intestine

Table 1. Sources of hepatic enzymes.

<Table 1>

Typically, ALP and GGT both rise in response to biliary injury (intra- or extra-hepatic), however ALP correlates with bone turnover in children, therefore GGT is used in preference as the main biliary enzyme during childhood. However, both normal and elevated GGT levels may be of diagnostic significance, as discussed below, particularly in differentiating intrahepatic cholestasis syndromes.

Liver 'function' tests

Hepatocytes synthesise the majority of all serum proteins, including albumin and clotting factors. Albumin is used as a medium-term marker of hepatic synthetic function[4] whilst INR (international normalised ratio) and PT (prothrombin time) can be used as short-term markers of synthetic capacity, if haematological causes and vitamin K deficiency have been ruled out. It should be remembered that INR was designed for monitoring of warfarin activity however is a useful method for standardising prothrombin time between laboratories.

Encephalopathy results from the accumulation of nitrogenous compounds and endogenous opioids, therefore elevation of ammonia is used in the diagnosis of hepatic encephalopathy. It has a good negative predictive value: hepatic encephalopathy is unlikely in the setting of a normal ammonia[5]. Urea cycle disorders should also be considered when ammonia level is elevated.

CASE 1:

A 6 week old infant is referred to the paediatric unit due to prolonged jaundice. She has pigmented stools, colour confirmed by the treating physician. Blood results: total bilirubin 168 $\mu\text{mol/L}$, conjugated bilirubin 140 $\mu\text{mol/L}$, ALT 150 IU/L, AST 161 IU/L, GGT 30 IU/L, Alb 36 g/L, INR 1.2.

Prolonged, conjugated jaundice

Prolonged jaundice is defined as visible jaundice at 14 days in term infants or 21 days in those born at less than 37 weeks. The most common cause for unconjugated hyperbilirubinaemia is breastfeeding associated jaundice, which may be present in 25-45% of breastfed neonates[6]. Whereas, there is a wide differential for conjugated hyperbilirubinaemia (where conjugated bilirubin comprises >20% of the total bilirubin or an absolute value of 25 $\mu\text{mol/L}$ [7,8], [see table 2](#)) as the neonatal liver has a tendency to develop cholestasis in response to a variety of insults. Initial investigation should focus on: confirming conjugated hyperbilirubinaemia, looking for evidence of acute liver failure or sepsis, and then investigating the cause ([table 2](#))[8]. Early discussion with a hepatology unit facilitates rapid investigation of time-critical diagnoses.

Test	Abnormality	Suggests a diagnosis of
------	-------------	-------------------------

Viral hepatitis serology	Positive results on serology	HSV, hepatitis A/B/C viruses
Congenital infection serology	Positive IgM CMV PCR (urine & blood)	Toxoplasma, rubella, CMV, HSV
Blood & urine culture	Bacterial growth	Sepsis
Immunoreactive trypsinogen (IRT) – under 2-3 weeks age	Raised IRT	Cystic fibrosis
Sweat test	Raised sweat chloride	
Alpha-1-antitrypsin levels and Pi type	PiZZ	Alpha-1-antitrypsin deficiency
Galactose-1-phosphate uridyl transferase	Low enzymatic activity	Galactosaemia
Thyroid function tests	Low T4, high TSH	Congenital hypothyroidism
Plasma amino acids	Raised tyrosine	Tyrosinaemia Non specific
Urine organic acids	Raised succinylacetone	Tyrosinaemia
Alpha fetoprotein	Significantly increased*	Hepatoblastoma, tyrosinaemia, or non-specific
Ultrasound abdomen	Absent or abnormal gall bladder	Biliary atresia
	Cyst of common bile duct	Choledochal cyst

Table 2. Initial investigations used in identifying causes of neonatal conjugated hyperbilirubinaemia. *Elevated alpha fetoprotein in neonates may be normal. CMV – cytomegalovirus; EBV – Epstein-Barr virus; HSV – herpes simplex virus; IRT – immunoreactive trypsin; PCR – polymerase chain reaction; TSH – thyroid-stimulating hormone

<Table 2>

Differential of conjugated hyperbilirubinaemia

Biliary atresia is an important cause of neonatal cholestasis, accounting for 25% of all neonatal conjugated hyperbilirubinaemia presenting to a tertiary centre, and early treatment significantly improves outcomes[9]. It typically presents with pale stools (not golden yellow or green; any other colour is compatible with diagnosis of biliary atresia), conjugated hyperbilirubinaemia, aminotransferases in the hundreds, and an elevated GGT. Physical inspection of the stool to confirm the pigment by healthcare professionals is strongly recommended.

The infant in this vignette has a conjugated hyperbilirubinaemia but her stools are pigmented and she has a low GGT. She is not in liver failure (and does not have vitamin K deficiency) given her normal INR. The pigmented nature of her

stools does not exclude cholestasis. However, the low GGT helps to narrow the differential diagnosis by favouring progressive familial intrahepatic cholestasis (PFIC). This infant will need referral to a liver centre for further management.

PFIC is a group of rare conditions caused by germline mutation of canalicular membrane transporters. PFIC type 1 may be associated with short stature, short digits, and diarrhoea. Bile Salt Export Protein (BSEP) deficiency (PFIC type 2) has no additional extra-hepatic phenotype. Though variable, the natural history of low GGT intrahepatic cholestasis is unremitting progression with end-stage liver in early childhood

CASE 2:

A 5 year old presents to A&E with sudden onset jaundice and malaise. Blood results: total bilirubin 190 $\mu\text{mol/L}$, conjugated bilirubin 170 $\mu\text{mol/L}$, ALT 850 IU/L, AST 800 IU/L, GGT 110 IU/L, Alb 35 g/L, INR 3.1. Repeat INR 4-hours after 2mg IV vitamin K is 3.0.

Acute liver failure

This girl has presented with acute liver failure (ALF), as identified by coagulopathy (INR >2.0) that is unresponsive to vitamin K associated with biochemical evidence of hepatocellular injury. An INR >1.5 with evidence of encephalopathy would also be classed as ALF. This is a medical emergency; any child with an abnormal INR and suspected ALF should be referred to a hepatology transplant unit urgently. The differential diagnosis of ALF includes: infectious causes, metabolic causes, drugs & toxins (paracetamol overdose), rarities, and indeterminate (non-A-E hepatitis). Initial investigations are listed in table 3[10].

Test	Abnormality	Suggests a diagnosis of
Viral hepatitis serology	IgM serology positive	Hepatitis A,B, & E, CMV, EBV, adenovirus, enterovirus
Serum caeruloplasmin	Low levels	Wilson disease
Serum copper	Elevated	
Haemoglobin and reticulocytes	Normocytic anaemia and raised reticulocytes	
Direct Coombs' test	Negative	
Urinary copper (pre-/post-penicillamine challenge)	Elevated urinary copper	
Autoantibodies	Positive ANA / ASMA / LKM / SLA / LC1	Autoimmune hepatitis
Immunoglobulins	Increased IgG	

Toxicology screen	Raised paracetamol level	Paracetamol overdose
Blood gas, serum amino acids, urinary organic acids, lactate, acyl carnitines, ammonia, mitochondrial DNA	Significant abnormalities	Metabolic diseases, including: mitochondrial, fatty acid oxidation defects, organic acidaemias, urea cycle defects

Table 3. Examples of initial blood investigations used in identifying the cause of acute liver failure. ASMA – anti-smooth muscle antibody; ANA – antinuclear antibody; EBV – Epstein-Barr virus; LKM – anti-liver-kidney microsomal antibodies; SLA – soluble liver antigen; LC1 – Liver cytosol 1 antigen.

<Table 3>

If there is no history of drug or toxin exposure, then the most likely causes are viral or metabolic. Viral causes include hepatitis A & E viruses (usually with history of travel to Asia or Africa). Cytomegalovirus, Epstein-Barr virus, and herpes simplex virus can cause ALF in immunocompromised patients.

Acute liver failure in infancy is more frequently due to metabolic disorders, including galactosaemia and tyrosinaemia. However, at 5 years old, Wilson disease may present acutely with Coombs' negative haemolysis, acute liver failure, and renal impairment.

Prognostic markers in ALF

Early identification of children who will not survive with their native liver allows more rapid listing for transplant. The prognostic markers for poor outcome with ALF secondary to paracetamol overdose are different to those for ALF due to other causes. In non-paracetamol ALF an INR >4 alone would be a poor prognostic marker, whereas in paracetamol-induced ALF, acidosis, renal impairment, raised lactate, and encephalopathy are more important. There is no correlation between ALT and outcome in all cases of ALF.

CASE 3:

A 13 year old girl presents with jaundice after generally feeling unwell for 1 month. Blood results: total bilirubin 96 µmol/L, conjugated bilirubin 80 µmol/L, ALT 300 IU/L, AST 290 IU/L, GGT 106 IU/L, Alb 18 g/L, total protein 40 g/L, INR 2.5, platelets 113x10⁹/L. 4 hours after 10mg IV phytomenadione, INR 1.1. Urinary copper 0.4 µmol/24-hours, serum caeruloplasmin 0.5 g/L.

Acute hepatic dysfunction, without liver failure

This teenager has presented with a short history of new-onset conjugated jaundice associated with elevated aminotransferases. She is not in acute liver failure as her INR normalised following vitamin K administration, suggesting vitamin K deficiency, which may be due to inadequate bile acid delivery to the gut. This is an acute-on-chronic presentation, as evidence by low albumin, and thrombocytopenia due to hypersplenism from portal hypertension.

The main differential diagnosis is between autoimmune hepatitis and Wilson disease. The initial investigations above point towards autoimmune hepatitis due to low albumin and elevated immunoglobulins. Infection should also be considered as a cause for raised IgG. The normal caeruloplasmin and 24-hour urinary copper make Wilson disease unlikely.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a rare condition of hepatic inflammation associated with circulating non-organ specific autoantibodies[11]. It demonstrates a good response to immunosuppression, which greatly improves the clinical outcome for affected children. There are three types of AIH, based upon the autoantibodies present (see table 4), though they have a similar clinical course.

The two most discriminatory laboratory investigations are immunoglobulin G (IgG) titre and high-titre non-organ-specific autoantibodies[11]. IgG is raised in 85-90% of all patients with AIH.

	Type I	Type II	Type III
Antibodies	Anti-SMA, ANA, pANCA	Anti-LKM1 /-LC1	Anti-LC/-SLA
Age	Peak at 10-20 and 45-70 years	2-14 years	Peak at 10-20 and 45-70 years
Increased IgG	↑↑↑	↑	↑↑
Associations	HLA B8, DR3, DR4	HLA DR7, DR3	

Table 4. Differences of type 1, 2, and 3 autoimmune hepatitis[12]. SMA – smooth muscle antibody; ANA – antinuclear antibody; LC1 – liver cytosol 1; LKM – Liver-kidney microsomal antigen; LP – liver-pancreas; pANCA – perinuclear anti-neutrophil cytoplasmic antibodies; SLA – soluble liver antigens

<Table 4>

Wilson disease

Other features needed to exclude an alternative diagnosis are a negative viral hepatitis screen and exclusion of Wilson disease (WD). Ruling out WD is challenging, though patients with WD may have higher bilirubin, ALT/AST in low hundreds, and low ALP. Caeruloplasmin is low in the majority of affected patients. It is not 100% sensitive (see table 5) [13] but it is the authors' clinical experience that most patients have caeruloplasmin <0.05g/L. Urinary copper should be high (with further elevation after penicillamine) but definitive diagnosis of WD needs genetics (for ATP7B mutation) or liver copper measurement.

Caeruloplasmin concentration cut-off (g/L)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
0.20	98	56	48	99
0.14	93	100	100	97
0.10	79	100	100	92

Table 5[13]. Data on the validity of use of 3 different cut-off thresholds of caeruloplasmin for diagnosis of Wilson disease in patients clinically suspected of having the condition.

<Table 5>

Patients with features suggestive of AIH should be referred to a tertiary liver centre, where a liver biopsy may be performed to confirm the diagnosis prior to starting treatment.

BOX 2. 'Dos and Don'ts' in suspected liver disease

Dos

- Check the prothrombin time (or INR)
- Discuss early with a hepatology centre
- Closely monitor liver function tests while awaiting a formal plan of management

Don'ts

- Use ALT or AST as a marker of hepatic function or severity of disease
 - Ignore unexplained abnormal LFTs, even in clinically well children
 - Assume a diagnosis without completing investigations (e.g. diagnosing NAFLD without fully excluding Wilson disease)
-

CASE 4:

A 15 year old is seen by the paediatric surgical team with vague abdominal pain. BMI 32.9 kg/m², BMI z-score +2.29, waist circumference 99th centile. Blood results: total bilirubin 13 µmol/L, ALT 110 IU/L, AST 101 IU/L, GGT 65 IU/L, Alb 35 g/L, INR 1.0.

Non-alcoholic fatty liver disease

This 15 year old has had incidental abnormalities LFT identified for which the most likely diagnosis is non-alcoholic fatty liver disease (NAFLD).

A careful history and examination should be undertaken for features of AIH, Wilson disease, and inborn errors of metabolism, as discussed above. An ultrasound demonstrating increased hepatic echogenicity (suggestive of fat infiltration), with a negative panel of secondary investigations (see table 6), and no history of alcohol intake would suggest a diagnosis of NAFLD in the context of an obese child, but specialist opinion is advised. Diagnosis can only formally be made by liver biopsy, which is also useful for staging disease.

Test	Abnormality	Suggests a diagnosis of
Viral hepatitis serology	IgG or IgM serology positive	Hepatitis B & C, EBV, CMV
Serum caeruloplasmin	Low levels	Wilson disease
Urinary copper	Elevated 24-hour excretion	
Autoantibodies	Positive ANA / ASMA / LKM / SLA / LC1	Autoimmune hepatitis
Immunoglobulins	Increased IgG	
Alpha-1-antitrypsin levels and Pi type	PiZZ	Alpha-1-antitrypsin deficiency
Oral glucose tolerance test	Raised fasting insulin, or impaired glucose tolerance	Insulin resistance
High-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG)	Low HDL, high LDL, high TG	Dyslipidaemia or lysosomal acid lipase disease

Table 6. Ancillary investigations used in excluding secondary causes of hepatic steatosis and to look for end-organ damage in NAFLD. ASMA – anti-smooth muscle antibody; ANA – antinuclear antibody; CMV – cytomegalovirus; EBV –

Esptein-Barr virus; LKM – anti-liver-kidney microsomal antibodies; SLA – soluble liver antigen; LC1 – Liver cytosol 1 antigen.

<Table 6>

Non-alcoholic fatty liver disease (NAFLD) describes a spectrum from isolated hepatic steatosis through non-alcoholic steatohepatitis (NASH) to fibrosis, ultimately leading to cirrhosis[14]. The condition is intimately related to obesity, insulin resistance, and the metabolic syndrome. Approximately 40% of obese children are affected with NAFLD[15]. Up to 9% of children with only ‘mildly’ abnormal LFT can have stage 3/4 fibrosis on biopsy[16] and 25% of those with stage 3/4 fibrosis have normal AST/ALT. There is no correlation between ALT and fibrosis; and fibrosis is the best marker of long-term outcome in adults[17]. This statement is true for many chronic liver diseases: normal AST and ALT give little information about progression of the condition.

Management of NAFLD

Long-term, patients with NAFLD are at increased risk of all complications of the metabolic syndrome, therefore children should be managed in accordance with guidance from the RCPCH Obesity Services for Children and Adolescents group[18].

There are no uniformly accepted pharmacological therapies recommended for paediatric NAFLD other than weight loss and exercise. Some suggested situations for when to refer to tertiary hepatology services are listed in **Box 1**[19].

BOX 3. When to refer children with suspected non-alcoholic fatty liver disease

- Diagnostic uncertainty
 - Non-obese
 - ALT or AST >1.5x upper limit of normal
 - Splenomegaly
 - Under 8 years of age
 - Evidence of hepatocellular dysfunction or portal hypertension
 - Persistently raised aminotransferases or gamma glutamyl transferase despite 3 months of lifestyle modification
-

BOX 1. ‘Red flags’ in suspected liver disease

- Any encephalopathy

- INR >1.5, which does not normalise with IV vitamin K
 - pH <7.3
 - Hypoglycaemia
 - High or rising lactate
 - High or rising creatinine or other evidence of renal dysfunction
 - Evidence of hepatocellular dysfunction (low albumin, hypoglycaemia)
 - Evidence of portal hypertension (splenomegaly, thrombocytopenia)
-

CONCLUSIONS

ALT/AST, bilirubin, and GGT should be thought of as a screen for acute hepatobiliary injury, though may be normal despite chronic liver disease. Whereas coagulation, glucose, albumin, and pH are more informative of physiological capacity. Diagnosis of specific pathologies requires an additional set of investigations with correlation to the clinical signs and symptoms of the patient.

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FIGURE LEGENDS

Figure 1. Six portal triads are arranged around a central vein in the classical hepatic lobule. A hepatic acinus illustrates the direction of blood flow. The zoomed image shows plates of hepatocytes lining a sinusoid. Bile drains in canaliculi in the opposite direction to blood flow, back towards the portal triad.

Figure 2. Measurement of direct conjugated and total bilirubin. Sodium benzoate is added to free bound unconjugated bilirubin in measurement of total bilirubin. Direct bilirubin predominantly reflects conjugated bilirubin however a proportion of unconjugated bilirubin is unbound, which will influence the result.

Figure 2. Bilirubin metabolism with the site pre-, intra-, and post-hepatic jaundice illustrated.